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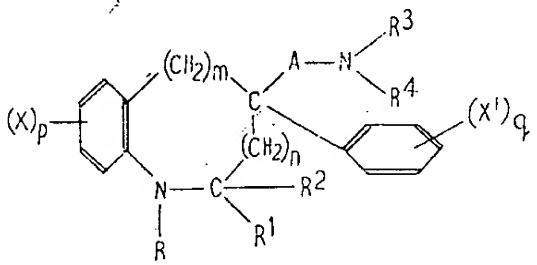
(72) Inventor JOHN KRAPCHO

(54) NOVEL QUINOLINE, BENZAZEPINE AND BENZAZOCINE DERIVATIVES AND THEIR PREPARATION

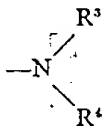
(71) We, E. R. SQUIBB & SONS INC. a Corporation organized under the laws of the State of Delaware, United States of America, of 909 Third Avenue, New York, New York 10022, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement: —

This invention relates to quinoline, benzazepine and benzazocine compounds and provides new compounds of the formula:



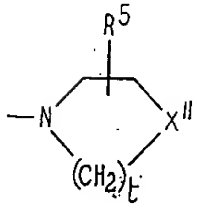
I

wherein X and X′ are the same or different and are hydroxy, lower alkyl, halogen, halo-lower alkyl, benzyloxy or lower alkoxy; R is lower alkyl, lower alkenyl, lower alkynyl, X-substituted aralkyl, aralkyl, or aralkenyl; R^1 and R^2 are each hydrogen or together are oxo (O=); A is alkylene; p and q are each 0, 1, 2 or 3; m is 1 or 2; n is 0 or 1; and



is a basic radical having less than 14 carbon atoms, in which R^3 and R^4 are the same or different and are hydrogen, lower alkyl, cycloalkylalkyl (e.g. cyclopropylmethyl), alkenyl (e.g. allyl or 3,3-dimethylallyl); alkynyl (e.g. propargyl), X-substituted phenyl; X-substituted thienyl; X-substituted furyl, X-substituted pyridyl, X-substituted aralkyl (e.g., 4-chlorophenethyl); or X-substituted cinnamyl; or R^3 and R^4 can together with the attached n atom, form a saturated heterocyclic radical having five to seven atoms in the ring. Heterocyclic radicals represented by NR^3R^4 are those having the formula:

[Price 25p]



in which X'' represents N—R⁶, CHR⁶, O or S, t represents 1, 2 or 3 and R⁵ and R⁶ represent hydrogen, lower alkyl, hydroxy-lower alkyl, alkanoyloxy-lower alkyl, alkanoyloxy-lower alkoxy-lower alkyl, hydroxy-lower alkoxy-lower alkyl, di(lower alkyl)-amino-lower alkyl, di(lower alkyl)amino-lower alkoxy-lower alkyl, X-substituted aryl or X-substituted aryl-lower alkyl. These may be exemplified by piperidino; (lower alkyl)piperidino, e.g., 2, 3 or 4-(lower alkyl)piperidino; (lower alkoxy)piperidino; pyrrolidino; (lower alkyl)-pyrrolidino; (lower alkoxy)pyrrolidino; morpholino; (lower alkyl)-morpholino; di(lower alkyl)morpholino; (lower alkoxy)morpholino; thiamorpholino; (lower alkyl)thiamorpholino; di(lower alkyl)-thiamorpholino; (lower alkoxy)thiamorpholino; piperazino; (lower alkyl)piperazino (e.g. N-methylpiperazino); di(lower alkyl)piperazino; (lower alkoxy)piperazino; (hydroxy-lower alkyl)piperazino [e.g., N-2-(hydroxyethyl)piperazino]; alkanoyloxy-lower alkyl-piperazino, e.g., N-(2-acetoxyethyl)piperazino, N-(2-heptanoyloxyethyl)piperazino or N-(2-dodecanoyloxyethyl)-piperazino; (hydroxy-lower alkoxy-lower alkyl)piperazino [e.g., N-(2-hydroxyethoxyethyl)piperazino]; di(lower alkyl)amino-(lower alkyl)piperazino [e.g., N-dimethylaminoethylpiperazino]; di(lower alkyl)amino-(lower alkoxy-lower alkyl)piperazino [e.g., N-(2-dimethylaminoethoxyethyl)piperazino]; and homopiperazino and substituted homopiperazino [e.g., N-ethylhomopiperazino, N-benzylhomopiperazino and N-(hydroxyethyl)homopiperazino].

Of special interest are compounds of Formula I wherein p is 0, q is 0, A is lower alkylene, R^3 and R^4 are lower alkyl groups, m is 2 and n is 0 or 1, or m is 1 and n is 1, and compounds in which p is 0, q is 0, A is lower alkylene, —NR^3R^4 is morpholino, m is 1 and n is 0, R being in each case as defined above and R^1 and R^2 together being oxo.

The preferred compounds are those wherein m is 1, n is 0, R^1 and R^2 together are oxo; R is lower alkyl; A is —CH_2CH_2— and —NR^3R^4 is diethylamino or morpholino.

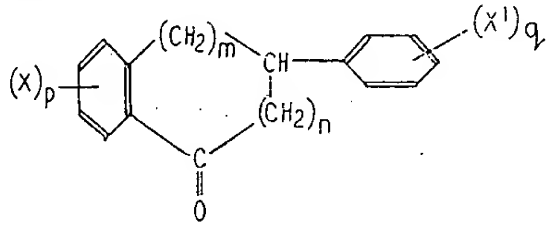
The terms "lower alkyl", "lower alkoxy", "lower alkenyl", "lower alkynyl" and "lower alkylene" as employed herein include both straight and branched chain radicals of up to eight carbon atoms and "halogen" is preefrably chlorine or bromine. The term "alkanoyloxy" includes radicals of up to fourteen carbon atoms.

The new bases of formula I form acid-addition salts by reaction with the common inorganic and organic acids. Such inorganic salts as the hydrohalides, e.g. hydrobromides, hydrochlorides and hydroiodides, sulphates, nitrates and phosphates, and such organic salts as the acetates, oxalates, tartrates, malates, citrates, succinates, benzoates, ascorbates, salicylates, theophyllinates, camphorsulfonates, alkanesulphonates, e.g. methanesulphonates, and arylsulphonates, e.g. benzenesulphonates and toluenesulphonates, are also within the scope of the invention. It is frequently convenient to effect the purification of the product by forming the acid-addition salt. The base may be obtained therefrom by neutralization with an alkali metal hydroxide such as sodium hydroxide.

The bases of formula I also form quaternary ammonium salts, e.g. by reaction with lower alkyl halides such as methyl chloride, methyl bromide or ethyl chloride, lower alkyl sulphates such as methyl sulphate or ethyl sulphate, and monocyclic aryl-(lower alkyl)halides and sulphates such as benzyl bromide or benzyl sulphate.

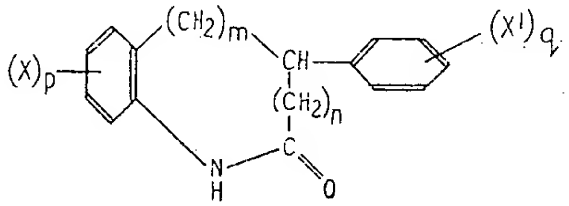
The compounds of this invention, including the optically active forms and the acid-addition salts thereof, are therapeutically active compounds which possess central nervous system stimulant activity and hence are utilizable in the treatment of depression, and also may be used for the control of obesity. Thus the compounds of this invention can be administered perorally, the dosage for such treatment being adjusted according to the activity of the particular compound employed. The dosage which may be administered may range from 0.01 to 100 mgs. per kg. of the mammalian host being treated.

The new compounds of formula I may be produced by initially converting a cyclic ketone of formula II:



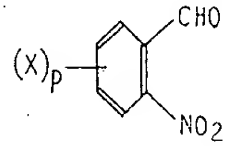
II

to a compound of formula III by treatment with sodium azide in a medium such as acetic acid, followed by concentrated sulphuric acid, or by conversion of II to an oxime and then rearranging the oxime to the desired compound of formula III by a Beckmann rearrangement, e.g. by treatment with an arylsulphonyl halide such as benzenesulphonyl chloride in a hydrogen halide acceptor, such as pyridine.



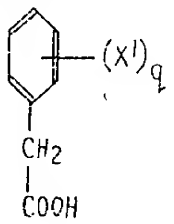
III

The compounds of Formula III wherein m=1 and n=0 may also be prepared by reacting a 2-nitro-benzaldehyde having formula IV:



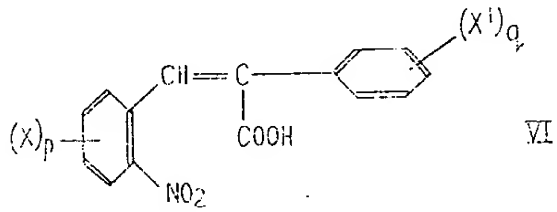
IV

with a phenylacetic acid having formula V:



V

to form a compound having formula VI:

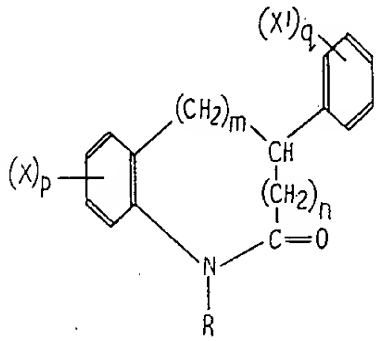


VI

The compound of formula VI is then cyclized by treatment with hydrogen in the presence of a catalyst such as palladium-carbon to form the lactam of formula III.

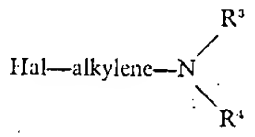
To form the compounds of formula I wherein R^1 and R^2 together are oxo from said lactam by a preferred procedure, the lactam III is then reacted with an appropriate agent to introduce the desired —R group. According to the identity of this group this agent may be, e.g., a dialkyl sulphate, such as dimethyl or dipropyl sul-

phate; an alkyl halide such as methyl bromide or propyl iodide; an alkenyl halide such as 6-chloro-1-hexene or 4-bromo-1-butene; an aralkyl halide such as benzyl bromide; or an aralkenyl halide such as 3-chloro-1-phenyl-1-propene or 4-bromo-1-phenyl-1-butene, in an inert solvent such as toluene, in the presence of a base such as sodamine, sodium hydride, potassium t-butoxide or powdered sodium hydroxide. In this way there is obtained the intermediate having the formula VII:



VII

wherein R, X, p and q are as defined above. This intermediate is then reacted in an inert solvent such as toluene in the presence of a base such as sodamide, potassium t-butoxide or powdered sodium hydroxide with an appropriate basic halide of the formula VIII



to yield the desired lactam of formula I (Hal being halogen, preferably chlorine or bromine).

The lactam so obtained may be reduced, e.g. by reacting it with lithium aluminium hydride, to form the corresponding compound of Formula I wherein R^1 and R^2 are hydrogen.

The following examples are illustrative of the invention. All temperatures are in degrees Centigrade.

Example 1

3-(2-Diethylaminoethyl)-3,4-dihydro-1-methyl-3-phenylcarbostyril, Hydrochloride

(A) Preparation of 3,4-dihydro-1-methyl-3-phenyl-carbostyril

A suspension of 22.0 g. of 3-phenylhydrocarbostyril in 200 ml. of toluene is added to a suspension of 3.9 g of sodamide in 250 ml. of toluene. The mixture is refluxed for thirty minutes, cooled to room temperature, and treated with 25.0 g. of dimethylsulfate. The mixture is refluxed for 2.5 hours, cooled, and treated with 200 ml. of water. The organic phase is washed with 100 ml. of water, dried over magnesium sulfate and filtered. Concentration of the filtrate to 50 ml., following by dilution with hexane until the solution becomes turbid, yields 19.3 g. of product, m.p. 85—95°. After purification of this material using acetonitrile and absolute alcohol, the product weighs 8.5 g., m.p. 95—97°.

(B) Preparation of 3-(2-diethylaminoethyl)-3,4-dihydro-1-methyl-3-phenylcarbostyril, hydrochloride

To a suspension of 1.7 g. of 50% sodium hydride in 85 ml. of dimethylformamide is added 8.3 g. of the product of part A. The mixture is stirred and heated at 80—85° for thirty minutes, cooled to 25° and treated with a solution of 6.8 g. of 2-diethylaminoethyl chloride in 25 ml. of toluene. This mixture is refluxed for four hours and the solvent removed under reduced pressure. The residue is treated with 100 ml. of water and 100 ml. of ether. The aqueous phase is discarded and the organic phase extracted with a cold solution of 5 ml. of concentrated hydrochloric acid in 100 ml. of water. The aqueous layer is separated, treated with a solution of 4 g. of

sodium hydroxide in 20 ml. of water and the free base extracted with ether. The ethereal solution is dried over magnesium sulfate, filtered and the solvent evaporated to give 3.2 g. of base. The latter is dissolved in 15 ml. of absolute alcohol, treated with 1.5 ml. of 7.7 N alcoholic hydrogen chloride and the solution diluted with 100 ml. of ether to give 2.0 g. of product, m.p. 195—198°. After recrystallization from 10 ml. of isopropyl alcohol, the colorless material weighs 1.5 g., m.p. 198—200°.

Example 2

4-(2-Diethylaminoethyl)-3,4,5,6-tetrahydro-1-methyl-4-phenyl-1-benzazocin-2(1H)-one, hydrochloride

Following the procedure of Example 1 but utilizing an equivalent amount of 3,4,5,6-tetrahydro-4-phenyl-1-benzazocin-2(1H)-one (prepared in accordance with the procedures set forth in U.S. patent specification No. 3,330,823 in lieu of 3-phenylhydrocarbostyril, the product recovered is 4-(2-diethylaminoethyl)-3,4,5,6-tetrahydro-1-methyl-4-phenyl-1-benzazocin-2(1H)-one, hydrochloride.

Example 3

4-(3-Piperidinopropyl)-3,4,5,6-tetrahydro-1-methyl-4-phenyl-1-benzazocine-2(1H)-one, hydrochloride

Following the procedure of Example 1 but utilizing an equivalent amount of 3,4,5,6-tetrahydro-4-phenyl-1-benzazocin-2-(1H)-one, in lieu of 3-phenylhydrocarbostyril in part A and 3-piperidinopropyl chloride in lieu of 2-diethylaminoethyl chloride in part B, the desired product is recovered.

Example 4

3-(2-Diethylaminoethyl)-4,5-dihydro-1-methyl-3-phenyl-1H-1-benzazepin-2(3H)-one, hydrochloride

Utilizing an equivalent quantity of 4,5-dihydro-3-phenyl-1H-1-benzazepin-2(3H)-one in lieu of 3-phenylhydrocarbostyril and otherwise following the procedure set forth in Example 1, the desired product is recovered.

Example 5

3-(3-Dimethylaminopropyl)-3,4-dihydro-1-methyl-3-phenylcarbostyril, hydrochloride

Substituting an equivalent amount of 3-dimethylaminopropyl chloride for the 2-diethylaminoethyl chloride used in Example 1 (B), there are obtained the free base and thereafter the desired salt.

Example 6

3-(3-Morpholinopropyl)-4,5-dihydro-1-methyl-3-phenyl-1H-1-benzazepin-2(3H)-one, hydrochloride

By substituting an equivalent quantity of 3-morpholinopropyl chloride in the procedure of Example 1(B) and 4,5-dihydro-3-phenyl-1H-1-benzazepin-2(3H)-one in lieu of 3-phenylhydrocarbostyril in the procedure of Example 1 (A); the desired product is recovered.

Example 7

4-(3-Piperidinopropyl)-3,4,5,6-tetrahydro-4-(*o*-chlorophenyl)-1-propyl-1-benzazocin-2(1H)-one, hydrochloride

(A) 3,4,5,6-Tetrahydro-4-(*o*-chlorophenyl)-1-propyl-1-benzazocin-2(1H)-one

Following the procedure of Example 1 (A) but utilizing 3,4,5,6-tetrahydro-4-(*o*-chlorophenyl)-1-benzazocin-2(1H)-one in lieu of 3-phenylhydrocarbostyril and propyl iodide instead of dimethylsulfate, a crystalline material is recovered.

(B) 4-(3-Piperidinopropyl)-3,4,5,6-tetrahydro-4-(*o*-chlorophenyl)-1-propyl-1-benzazocin-2(1H)-one, hydrochloride

3,4,5,6- - Tetrahydro - 4 - (*o* - chlorophenyl) - 1 - propyl - 1 - benzazocin-2(1H) - one is reacted with 3-piperidinopropyl chloride in the manner described in Example 1 (B) to give a crystalline material.

Example 8

4-[2-(1-Hexamethylenimino)ethyl]-3,4,5,6-tetrahydro-1-benzyl-4-*o*-tolyl-1-benzazocin-2(1H)-one, hydrochloride

(A) 3,4,5,6-Tetrahydro-1-benzyl-4-*o*-tolyl-1-benzazocin-2(1H)-one

Substituting an equivalent quantity of 3,4,5,6-tetrahydro-4-*o*-tolyl-1-benzazocin-2(1H)-one for 3-phenylhydrocarbostyril and benzyl chloride in lieu of dimethylsulfate in the procedure of Example 1 (A), a crystalline material is recovered.

(B) 4-[2-(1-Hexamethylenimino)ethyl]-3,4,5,6-tetrahydro-1-benzyl-4-*o*-tolyl-1-benzazocin-2(1H)-one, hydrochloride

3,4,5,6-Tetrahydro-1-benzyl-4-*o*-tolyl-1-benzazocin-2(1H)-one is reacted with 2-(hexamethylenimino)ethyl chloride in the manner described in Example 1 (B) to give a crystalline material.

Example 9

3-[3-(4-Methylpiperazino)propyl]-4,5-dihydro-1-methyl-3-*o*-methoxyphenyl-1H-1-benzazepin-2(3H)-one, hydrochloride

(A) 4,5-Dihydro-1-methyl-3-*o*-methoxyphenyl-1H-1-benzazepin-2(3H)-one

Following the procedure of Example 1 (A) but substituting 4,5-dihydro-3-*o*-methoxyphenyl-1H-1-benzazepin-2(3H)-one, for 3-phenylhydrocarbostyril there is obtained a crystalline product.

(B) 3-[3-(4-Methylpiperazino)propyl]-4,5-dihydro-1-methyl-3-(*o*-methoxyphenyl)-1H-benzazepin-2(3H)-one, hydrochloride

By substituting 3-(4-methylpiperazino)propyl chloride for the diethylaminoethyl chloride in the procedure of Example 1 (B) there is obtained a crystalline product.

Example 10

4-(2-Diethylaminoethyl)-3,4,5,6-tetrahydro-8,9-dimethoxy-1-methyl-4-(*p*-methoxyphenyl)-1-benzazocin-2(1H)-one, hydrochloride

By replacing the 3-phenylhydrocarbostyril with 3,4,5,6-tetrahydro-8,9-dimethoxy-4-(*p*-methoxyphenyl)-1-benzazocin-2(1H)-one in the procedure of Example 1, there is obtained 4 - (2 - diethylaminoethyl) - 3,4,5,6 - tetrahydro - 8,9 - dimethoxy - 1-methyl - 4 - (*p* - methoxyphenyl) - 1 - benzazocin - 2(1H) - one, hydrochloride.

Example 11

3-(2-Diethylaminoethyl)-4,5-dihydro-7,8-dimethoxy-1-methyl-3-(*p*-methoxyphenyl)-1H-1-benzazepin-2(3H)-one, hydrochloride

By replacing 3-phenylhydrocarbostyril with 4,5-dihydro-7,8-dimethoxy-3-(*p*-methoxyphenyl)-1H-1-benzazepin-2(3H)-one in Example 1, there is obtained 3-(2-diethylaminoethyl)-4,5-dihydro-7,8-dimethoxy-1-methyl-3-(*p*-methoxyphenyl)-1H-1-benzazepin-2(3H)-one, hydrochloride.

Example 12

3-(2-Diethylaminoethyl)-4,5-dihydro-1-methyl-3-(*p*-methoxyphenyl)-8-methyl-1H-1-benzazepin-2(3H)-one, hydrochloride

By replacing the 3-phenylhydrocarbostyril with 4,5-dihydro-3-(*p*-methoxyphenyl)-8-methyl-1H-1-benzazepin-2(3H)-one in Example I, there is obtained 3 - (2 - dimethaminoethyl) - 4,5 - dihydro - 1 - methyl - 3 - (*p* - methoxyphenyl) - 8 - methyl-1H - 1 - benzazepin - 2(3H) - one, hydrochloride.

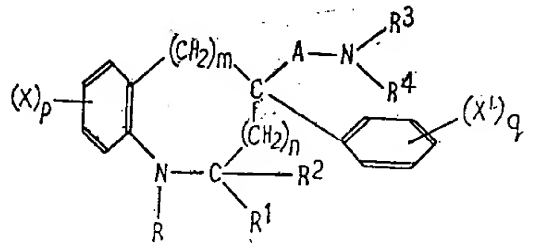
Example 13

3-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-1-methyl-3-phenyl-quinoline

Treating 5.0 grams of the product of Example 1 (B) with lithium aluminium hydride yields 3 - [2 - (diethylamino)ethyl] - 1,2,3,4 - tetrahydro - 1 - methyl - 3-phenyl - quinoline.

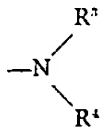
WHAT WE CLAIM IS:—

1. A compound having the formula:

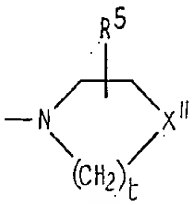


wherein p and q are each 0, 1, 2 or 3; m is 1 or 2; n is 0 or 1; X and X' are the same or different and are hydroxy, lower alkyl, halogen, halo-lower alkyl, benzyloxy

or lower alkoxy; R is lower alkyl, lower alkenyl, lower alkynyl, X-substituted aralkyl, aralkyl or aralkenyl; R^1 and R^2 are each hydrogen or together are oxo; A is alkylene;



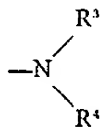
is a basic radical of less than fourteen carbon atoms wherein R^3 and R^4 are the same or different and are hydrogen, lower alkyl, cycloalkylalkyl, alkenyl, alkynyl, X-substituted phenyl; X-substituted thienyl; X-substituted furyl, X-substituted pyridyl; X-substituted aralkyl; or X-substituted cinnamyl; or R^3 and R^4, together with the attached N atom, form a saturated heterocyclic radical having the formula:



in which X'' represents N—R^6, CHR^6, O or S, t represents 1, 2 or 3 and R^5 and R^6 represent hydrogen, lower alkyl, hydroxy-lower alkyl, alkanoyloxy-lower alkyl, alkanoyloxy-lower alkoxy-lower alkyl, hydroxy-lower alkoxy-lower alkyl, di(lower alkyl)amino-lower alkyl, di(lower alkyl)amino-lower alkoxy-lower alkyl, X-substituted aryl or X-substituted aryl-lower alkyl.

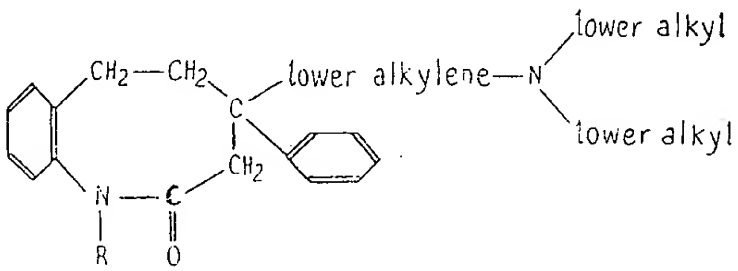
2. A compound according to claim 1, wherein —NR^3R^4 is: piperidino; (lower alkyl)piperidino; (lower alkoxy)piperidino; pyrrolidino; (lower alkyl)-pyrrolidino; (lower alkoxy)pyrrolidino; morpholino; (lower alkyl)-morpholino; di(lower alkyl)morpholino; (lower alkoxy)morpholino; thiamorpholino; (lower alkoxy)thiamorpholino; di(lower alkyl)-thiamorpholino; (lower alkoxy)thiamorpholino; piperazino; (lower alkyl)piperazino; di(lower alkyl)-piperazino; (lower alkoxy)piperazino;(hydroxy-lower alkyl)piperazino; alkanoyloxy-lower alkyl-piperazino; (hydroxy-lower alkoxy-lower alkyl)piperazino; di(lower alkyl)amino-(lower alkyl)piperazino; di(lower alkyl)amino-(lower alkoxy-lower alkyl)piperazino; homopiperazino or substituted homopiperazino.

3. A compound according to claim 1, wherein m is 1, n is 0, R is lower alkyl, R^1 and R^2 together are oxo, A is —CH_2CH_2— and



is diethylamino or morpholino.

4. A compound according to claim 1 having the formula:

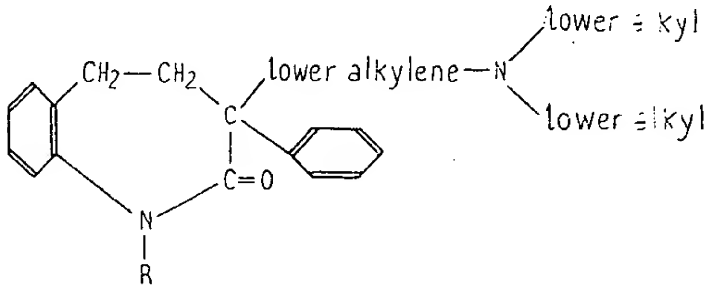


wherein R is as defined in claim 1.

5. 4 - (2 - diethylaminoethyl) - 3,4,5,6 - tetrahydro - 1 - methyl - 4 - phenyl-1 - benzazocin - 2(1H) - one.

6. 4 - (3 - piperidinopropyl) - 3,4,5,6 - tetrahydro - 1 - methyl - 4 - phenyl-1 - benzazocin - 2(1H) - one.

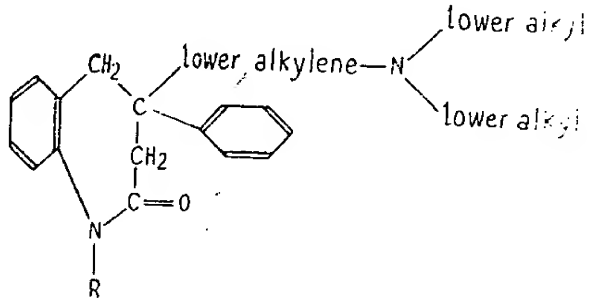
7. A compound according to claim 1 having the formula:



wherein R is as defined in claim 1.

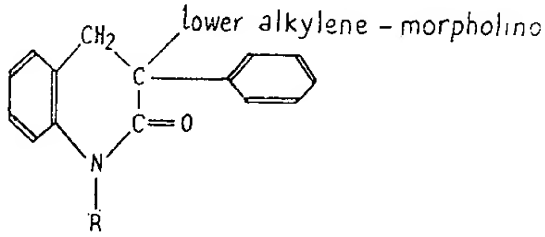
8. 3 - (2 - diethylaminoethyl) - 4,5 - dihydro - 1 - methyl - 3 - phenyl - 1H-1 - benzazepin - 2(3H) - one.

9. A compound according to claim 1 of the formula:



wherein R is as defined in claim 1.

10. A compound according to claim 1 of the formula:



wherein R is as defined in claim 1.

11. 3 - (2 - diethylaminoethyl) - 1,2,3,4 - tetrahydro - 1 - methyl - 3 - phenyl-quinoline, hydrochloride.

12. 3 - (2 - diethylaminoethyl) - 3,4 - dihydro - 1 - methyl - 3 - phenylcarbostyril, hydrochloride.

13. 4 - (3 - piperidinopropyl) - 3,4,5,6 - tetrahydro - 4 - (*o* - chlorophenyl)-1 - propyl - 1 - benzazocin - 2(1H) - one.

14. 3 - (3 - dimethylaminopropyl) - 3,4 - dihydro - 1 - methyl - 3 - phenylcarbostyril.

15. 3 - (3 - morpholinopropyl) - 4,5 - dihydro - 1 - methyl - 3 - phenyl - 1H-1 - benzazepin - 2(3H) - one.

16. 4 - [2 - (1 - hexamethylenimo)ethyl] - 3,4,5,6 - tetrahydro - 1 - benzyl - 4-*o* - tolyl - 1 - benzazocin - 2(1H) - one.

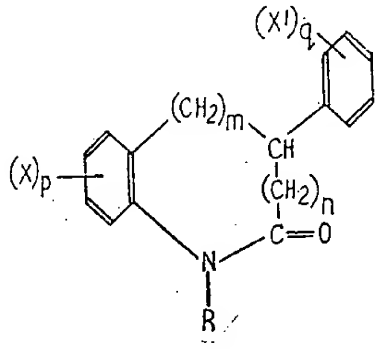
17. 3 - [3 - (4 - methylpiperazino)propyl] - 4,5 - dihydro - 1- methyl - 3 - *o*-methoxyphenyl - 1H - 1 - benzazepin - 2(3H) - one.

18. 4 - (2 - diethylaminoethyl) - 3,4,5,6 - tetrahydro - 8,9 - dimethoxy - 1-methyl - 4 - (*p* - methoxyphenyl) - 1 - benzazocin - 2(1H) - one.

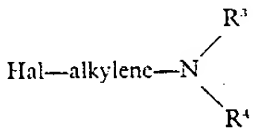
19. 3 - (2 - diethylaminoethyl) - 4,5 - dihydro - 7,8 - dimethoxy - 1 - methyl-3 - (*p* - methoxyphenyl) - 1H - 1 - benzazepin - 2(3H) - one.

20. 3 - (2 - diethylaminoethyl) - 4,5 - dihydro - 1 - methyl - 3 - (*p* - methoxyphenyl) - 8 - methyl - 1H - 1 - benzazepin - 2(3H) - one.

21. A process for preparing compounds as defined by claim 1, wherein R^1 and R^2 together are oxo, which comprises reacting compounds of the formula:



wherein R, X, X', m, n, p and q are as defined in claim 1, in an inert solvent in the presence of a base, with a basic halide of the formula:



where Hal is halogen and R^3 and R^4 are as defined in claim 1.

22. A process for preparing a compound of Formula I in which R^1 and R^2 are hydrogen atoms, which comprises treating a compound of said formula, in which R^1 and R^2 together are oxo, with a reducing agent to reduce said group to a methylene group.

23. A process according to claim 22 in which said compound in which R^1 and R^2 together are oxo is prepared by the process claimed in claim 21.

24. A process according to claim 22 wherein the said compound in which R^1 and R^2 together are oxo is a compound claimed in any of claims 5, 6, 8 or 12 to 20.

25. A compound as claimed in claim 1 and substantially as herein described.

26. A process according to claim 21 or 22 substantially as herein described.

27. A compound as claimed in any of claims 1 to 20 and 25 when prepared using a process as claimed in any of claims 21 to 24 and 26.

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